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Major review

Treatment of cystic macular lesions in hereditary retinal dystrophies

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ABSTRACT

Cystic macular lesions frequently contribute to impaired visual acuity in hereditary retinal dystrophies. Their pathogenesis varies and is not entirely understood. Carbonic anhydrase inhibitors have proven to be potentially efficacious, although not in all cases. We discuss the various factors and mechanisms implicated in the etiology of cystic macular lesions (anatomical abnormalities, impairment of the blood–retinal barrier, tangential vitreous traction, and mutations in retinoschin, etc.) and the various treatments that have been proposed.

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1. Introduction

Macular edema is a final common pathway for numerous insults within the eye, including traumatic, vascular, inherited, and inflammatory diseases.[25,127,144,157] These insults alter the capillary endothelial barrier, the function of Müller cells, the balance between ocular pressure, perfusion and both intraocular and intracellular fluid pressures,[30] and cell to cell adhesion.[114]

Macular edema was already described in detail by the time of World War I. Reports from 1870 on were mainly concerned with diabetic macular edema.[121] Subsequently it became known that other conditions could induce similar changes at the fovea.[195] In 1896, Nuel et al coined the term "oedème maculaire" to describe a histopathological specimen from a retinitis pigmentosa (RP) patient.[122] This observation was later confirmed by Ginsberg and Stock.[64,173]

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Today cystic macular edema (CME) represents a known pathologic complication in patients with hereditary retinal degenerations such as RP, X-linked retinoschisis, enhanced S-cone syndrome, choroideremia, and gyrate atrophy. CME is characterized by a localized expansion of the macular intracellular and/or extracellular space.

No known therapy halts the photoreceptor cell degeneration in inherited retinopathies. Nonetheless, the CME that occurs in such patients can be managed. We review the pathogenesis and diagnostic test modalities for detection and monitoring of cystoid macular lesions with an emphasis on current therapeutic options.

2. Pathogenesis of Cystic Macular Lesions

Although cystic macular lesions may contribute to blurred vision and visual loss in a variety of retinal disorders, their pathogenesis is not entirely understood.

Various pathogenetic hypotheses have been offered to explain the cystic macular lesions in retinal dystrophies (Figs. 1, 2). Impairment of the blood–retinal barrier[38,52,101,105] and the role of tangential vitreous traction[175] have been associated with CME in patients with RP. In X-linked retinoschisis and the enhanced S-cone syndrome the development of cystic-appearing macular changes is more likely related to disruption of retinal architecture by defects in cell to cell adhesion.[102,114] The absence of macular leakage on fluorescein angiography (FA), particularly in patients with X-linked retinoschisis, suggests that vascular leakage plays a minor role, if any, in their development.[47] The macular region has a predilection to develop these changes because of its unique structural features that include the absence of multiple supportive retinal layers.[51]

2.1. *The role of the blood–retinal barrier in cystoid macular edema*

The blood–retinal barrier (BRB) consists of an inner and an outer component. The inner BRB is formed by the retinal vascular endothelial cells and is established by complex tight junctions between these cells and a paucity of intraendothelial cell vesicles. The establishment and maintenance of the inner BRB is controlled by the perivascular astrocytes.

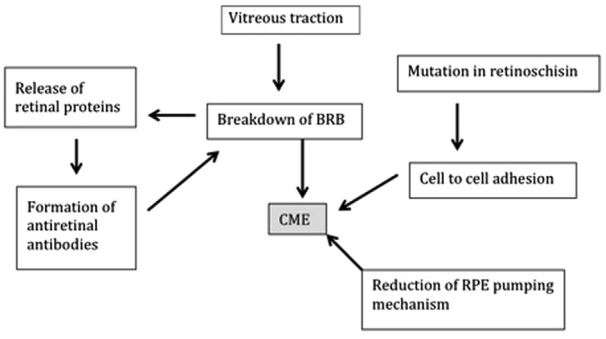

Fig. 1 – Diagram of the pathogenesis of cystoid macular edema.

Pericytes also influence the inner BRB, but their role is less clear.[186] The outer BRB is established by tight junctions between retinal pigment epithelial (RPE) cells that prevent fluids from the choroidal vessels to enter the retina and by an asymmetrical distribution of proteins that regulate vectorial transport across the RPE.[186]

The mechanisms of cystoid macular lesions in RP are not well defined, although an increase in BRB permeability at the levels of both the inner and outer BRBs has been identified.[38,101,105] In two separate reports, Fishman et al[38] and Mallick et al[105] demonstrated, by means of vitreous fluorophotometry, that eyes with RP have abnormalities in the BRB, with a tendency to a greater breakdown of the barrier in eyes with more extensive photoreceptor, RPE, and choriocapillaris deterioration. Their findings further suggest that either the inner BRB (at the level of retinal blood vessels) or outer BRB (at the level of the RPE) or both might be dysfunctional in affected patients and carriers of X-linked RP.[38,105] In the Royal College of Surgeons rat model for inherited retinal degeneration, there is disruption of the RPE tight junctions and increased permeability to horseradish peroxidase, which is associated with increased vesicular transport. Furthermore, horseradish peroxidase extravasates from outer retinal capillaries, apparently because of increased transendothelial vesicular transport.[19]

A compromise of the BRB is also indicated by the finding of sialoadhesin-positive microglia from 14 postnatal days in rds (retinal degeneration slow) mice retinas.[85,135] In the healthy central nervous system microglia of the rds mice that were protected by the BRB were sialoadhesin-negative, and sialoadhesin was entirely absent in wild-type retina. At earlier stages of rds retinal degeneration, when there was already significant increased microglial activity, there was sialoadhesin expression. By 21 postnatal days approximately 50% of microglia were sialoadhesin-positive. Sialodhesin is one of a group of macrophage-restricted cell surface sialic acid receptor proteins named siglecs that are highly conserved between rodents and humans. Although sialoadhesin is not thought to be a phagocytic receptor, its expression may facilitate other phagocytic receptors and increase cell–cell and cell–matrix adhesion.[85]

Using ocular spectrofluorometry, the kinetics of the inward leakage of fluorescein and its metabolite fluorescein glucuronide across the BRB can be assessed objectively after an intravenous bolus injection of a fluorescent solution.[101] Larsen et al,[101] using this method, advocate that pathological leakage is caused by enlargement of pre-existing water-filled pores or by establishment of new pores, rather than penetration by diffusion through the lipid bilayer of cellular membranes.

Furthermore, it is possible that the pathogenesis of CME involves a reduction of the RPE pumping mechanism.[81] A dysfunction of anticarbonic anhydrase and enolase activity by autoantibodies may be causally related to the formation of macular edema in some instances. Some have observed a relationship between CME in RP patients and the presence of circulating antiretinal antibodies.[81,197] Heckenlively et al[81] speculated that a breakdown of the BRB during the retinal degenerative process could release retinal proteins into the circulation that could be antigenic. This may explain how

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